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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,370	LAL ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7,9,11,13-15,27,28 and 46-53* is/are pending in the application.

4a) Of the above claim(s) *13-15,27 and 28* is/are withdrawn from consideration.

5)☒ Claim(s) *3-7, 9, 47 and 48* is/are allowed.

6)☒ Claim(s) *11,46 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed August 22, 2003 amending the specification to delete the embedded hyperlink and/or other form of browser-executable code, inserting Tables 1-7 before the claims and replacing "GenBank ID g181382" on page 22, line 18, with "GenBank ID 181382" has been entered.

Claims 3-7, 9, 11, 13-15, 27, 28 and 46-53 are pending. Claims 13-15, 27 and 28 are withdrawn. Claims 3-7, 9, 11 and 46-53 are under consideration.

Specification

The specification is objected to because of the following.

While the new pages containing Tables 1-7 filed August 22, 2003 were inserted before the claims, Tables 1-7 filed concurrently with the specification on July 12, 2001 were not canceled. Thus, the specification currently contains two sets of the tables.

Furthermore, the description of the tables is given on page 7 while the tables start on page 72.

See 37 CFR § 1.58 for regulation regarding tables.

Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 49-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11 and 49-50 are drawn to a naturally-occurring polynucleotide variant that is at least 95% or 98% identical to SEQ ID NO:2. Therefore the claims are directed to a genus of naturally-occurring variants, or alleles, of SEQ ID NO:2.

Naturally occurring nucleotide sequences having at least 95% identity to SEQ ID NO: 2 encode variants the function of which **may or may not be altered**. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the structure of any naturally occurring alleles. The general knowledge in the art concerning alleles dose not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others.

Thus, a naturally-occurring polynucleotide variant that is at least 95% or 98% identical to SEQ ID NO:2 encoding a polypeptide having undisclosed function lacks sufficient written description needed to practice the invention of claims 11 and 49-50.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA encoding SEQ ID NO:1 and fragments consisting of 750 contiguous nucleotides of SEQ ID NO:2 or nucleotides 843-1582 thereof, does not reasonably provide enablement for a DNA comprising 750 contiguous nucleotides of SEQ ID NO:2 or nucleotides 843-1582 thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 51-53 comprise two embodiments: first, DNAs encoding variants having the function of SEQ ID NO:1 and second, DNAs encoding variants lacking the P450 function of SEQ ID NO:1 and having undisclosed functions.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

With regard to the first embodiment, fragments comprising 750 contiguous nucleotides of SEQ ID NO:2 or nucleotides 843-1582 thereof are highly unlikely to encode cytochrome P450 activity and the specification does not teach otherwise. The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that comprises any of the above fragments of SEQ ID NO:2 because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptide structure having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Furthermore, the second embodiment of claims 51-53 encompass DNAs encoding polypeptides having no known functions. While it is known in the art and is taught in the specification that the fragments themselves can be used as probes, the claims encompass DNAs of unknown structure and unknown homology to SEQ ID NO:2 comprising said fragments and encoding inactive variants. The specification does not teach how to use said inactive variants. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The state of the art does not allow the predictability of the properties based on the structure. Therefore, one skilled in the art would require guidance as to how to use a DNA of unknown homology to SEQ ID NO:2 comprising 750 contiguous nucleotides of SEQ ID NO:2 or nucleotides 843-1582 thereof and encoding a polypeptide of undisclosed function in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

Claims 11, with dependent claims 46, 49 and 50, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite % identity. The specification teaches that "percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID NO number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only" (page 14, lines 8-12). Therefore, without knowing the entire specific sequence or a specific fragment thereof over which the percent identity is measured (as in claim 3, for example), it is impossible to know the metes and bounds of the claims. The specification states that "Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing" (page 10, lines 24-25). Thus, complementarity is not required to be 100% over the full-length sequence. In view of this, the metes and bounds of "complementary" are indefinite as well.

Furthermore, the prior art that discloses the sequences having the homology that is very close to the claimed homology. It is impossible to make an accurate comparison of the two highly homologous sequences without knowing the program and the algorithms and the parameters that are used.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11, 49 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Jaiswal et al.

Jaiswal et al. (GenBank accession Z00036, form PTO-1449, references 3, 18, 24) teach a DNA encoding human cytochrome P3(450) that is 93.6% (best local similarity of 97.5%) identical to SEQ ID NO:2, a vector containing it and a cell expressing thereof. The rejection is made in view of the indefiniteness of the claims, *supra*.

Furthermore, the claims recite "a polynucleotide complementary to the polynucleotide" comprising a naturally-occurring polynucleotide sequences at least 95% or 98% identical to the polynucleotide sequence of SEQ ID NO:2. In view of the

indefiniteness of the percent identity and complementarity discussed above, the sequence taught by Jaiswal et al. anticipates the claimed sequences.

Allowable Subject Matter

Claims 3-7, 9, 47 and 48 are allowed.

Response to Arguments

Applicant's arguments filed August 22, 2003 have been fully considered but they are not persuasive.

With regard to the specification, Applicants argue that "a skilled artisan would understand that GenBank identifiers may be either a numeral or a combination of the numeral preceded by the lower case letter "g" (Remarks, page 12, last paragraph). This is not agreed with because if "g181382" is used as a GI number, no sequence can be retrieved from GenBank database.

With regard to the utility rejection, Applicants argue that the patentable utility of polynucleotides is based on their use in cDNA microarrays and gene expression monitoring applications providing the Bedilion Declaration attesting to such uses (Remarks, pages 13-27). It appears that Applicants do not specifically argue the pending claims but provide general arguments that are applicable to all expressed genes. In addition, no pending claim is drawn to a microarray.

Applicants further argue, an invention can be a member of a class, where all the members of the class share a common utility (page 27-28). Applicants assert that "the Office action has not presented any evidence that the class of cytochrome P450 proteins has any, let alone a substantial number, of useless members, the Office Action must conclude that there is a "substantial likelihood" that the CYTPV encoded by the claimed polynucleotides is useful. It follows that the SEQ ID NO:2 polynucleotides is useful" (page 28, 2nd paragraph).

The point of rejection was not that there are useless cytochrome P450 proteins. The point of the rejection was that while cytochrome P450 proteins are known to act on "a broad group of structurally unrelated compounds including drugs, environmental pollutants, procarcinogens and endogenous substrates" (Sakuma et al. (1997), form PTO-1449 filed December 7, 2001, reference 8), the specification discloses that the cytochrome P450 of the instant invention acts at least on aniline or testosterone (pages 70-71). However, it appeared that according to Hayashi et al. (EP 0644 267 A2, form PTO-892 mailed November 19, 2002), the highly homologous cytochrome P450 CYP1A2 (99.3% identity to SEQ ID NO:1) does not act on testosterone and therefore, the specificity of the instant cytochrome P450 is unknown. While Applicants do not argue or even refer to this point of the rejection, the examiner further considered the following. The specification teaches that "the nearest GenBank homolog for the polypeptide of the invention", i.e. SEQ ID NO:1, as Genbank ID NO: 181382 (page 7,

lines 19-20 and Table 2). Said GenBank entry discloses the human cytochrome P450, CYP1A2 that according to the PTO search has 98.7% identity to SEQ ID NO:1 of the instant invention and the gap within the fragment P42-L499). CYP1A2 is well studied and its activity has been measured in relation to various compounds such as heterocyclic amines, for example (e.g., Sengstag et al. (1994), PTO-1449 filed December 7, 2001, reference 5, Sakuma et al. (1997),ibid, supra). *Therefore, it is reasonable to expect that the cytochrome P450 of the instant invention acts on aniline and other substrates that can be found within the same pool of compounds as CYP1A2.* There are no data providing the evidence to the contrary. Following these considerations, the 101 utility rejection and corresponding 112, 1st paragraph, rejection are withdrawn.

With regard to the written description, applicants argue that 'there is no requirement that the claims recite the functions of particular variants because the claims already provide sufficient structural definition of the claimed subject matter. That is, the claimed variants are defined in terms of SEQ ID NO:2. Because the claimed variants are defined in terms of SEQ ID NO:2, the precise chemical structure of every variant within the scope of the claims can be discerned" (page 34, last paragraph). This is not persuasive because it is not SEQ ID NO:2 or any specific variant what is claimed but a genus of molecules. For this genus the correlation between function and structure that is common to all members of the genus is not disclosed. The specification teaches

SEQ ID NO:1 having the function of the cytochrome P450. However, other species within the claimed genus may not have this activity or have other activities. Furthermore, the specification does not teach how to distinguish between a man made variant and a naturally-occurring variant falling within the scope of the genus.

With regard to the enablement rejection, Applicants argue that "the specification has provided enablement for polynucleotides comprising fragments of SEQ ID NO:2. For example, the specification discloses that oligomers which "contain a fragment of a polynucleotide encoding CYTPV" (i.e., a polynucleotide "comprising" a fragment of a polynucleotide encoding CYTPV) can be used in diagnostic assays (Specification, e.g., at page 50, lines 12-18). In another example, the specification discloses that an oligonucleotide can be labeled, thus creating a hybridization probe which is essentially a polynucleotide "comprising" the oligonucleotide (e.g., at page 47, line 33 to page 48, line 4; and page 63, line 31 to page 64, line 7). One of skill in the art would understand how to make and use polynucleotide "comprising' the recited fragments of SEQ ID NO:2, without an explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter" (page 35, last paragraph). This is not persuasive because with regard to diagnostics, neither the specification nor the art teach or suggest any condition that can be diagnosed. With regard ti the use as probes to detect the presence of a polynucleotide comprising SEQ ID NO:2", this is correct with regard to the fragment consisting of 750 contiguous nucleotides of SEQ ID

NO:2 or nucleotides 843-1582 thereof. However, the claims are not limited to such fragments and encompass DNAs of unknown structure comprising said fragments and encoding unknown function. The sequences comprising the claimed fragments when they are of an unknown structure and length cannot be used as probes. The claims also encompass polynucleotides encoding cytochrome P450s. 750 nucleotides constitute less than 42% of SEQ ID NO:2. This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants encoding cytochrome P450 requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification for the reasons indicated in the rejection above. Furthermore, while it possible to make various variants, one of ordinary skill in the art would not know how to use variants comprising the requisite fragments wherein said variants have an undisclosed function.

With regard to the 112, 2nd paragraph, rejection, Applicants argue with references to case law that "the standard for "definiteness" is that the claims define patent subject matter with a **reasonable** degree of precision and particularity" (page 36, last paragraph). This is not ;persuasive because unlike in the cited case law, percent identity is essential for defining the scope of the claimed subject matter and distinguishing it from the prior art. Applicants argue that "the Examiner, being a skilled artisan, was able to reasonably determine the % identity between the polynucleotide of Jaiswal et al. and the SEQ ID NO:2 polynucleotide, despite the alleged lack of disclosure of the programs, algorithms, and parameters to be used in such a determination. This is compelling evidence that the claims meet the requirement of 35 U.S.C § 112, second paragraph" (page 37, penultimate paragraph). This is not persuasive because the sequence search presented by the examiner used the specific program, algorithms, and parameters indicated at the sequence search. The pint made by the examiner was that while knowing the exact program, etc is not always necessary, in the instant case it is need because there is a very close prior art and the percent identity can slightly vary depending on programs, algorithms, and parameters. Applicants further argue that "the specification provides examples of programs, algorithms, and parameters that would allow a skilled artisan to reason ably determine the % identity between two sequences " (page 37, last paragraph). This is not

persuasive because the claims are not limited to the % identity measured by a specific method.

Thus, Applicants' arguments support the examiner's position that the prior art anticipates the claimed subject matter with "a **reasonable** degree of precision and particularity".

With regard to the 102(b) rejection, Applicants argue that "the polynucleotide variants recited by claims 11, 49 and 50 are not taught by Jaiswal et al. Claims 11 and 49 recite polynucleotide variants at least **95%** identical to SEQ ID NO:2, and claim 50 recites polynucleotide variants at least **98%** identical to SEQ ID NO:2. Jaiswal et al. do **not** teach polynucleotides at least 95% identical to SEQ ID NO:2, or polynucleotides at least 98% identical to SEQ ID NO:2. Therefore, Jaiswal et al do not anticipate the polynucleotide variants of claims 11, 49 and 50, and withdrawal of this rejection is requested" (page 39). This is not persuasive because it appears to be contradictory to Applicants own position discussed above in the 12, 2nd paragraph, arguments.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

November 7, 2003